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The Reliability of Functional Brain Connectivity as a Biomarker in the Prediction of Suicide Risk in Neurodegenerative Disease Populations: A Literature Review

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Abstract

Introduction: Neurodegenerative diseases, typically appearing in middle- to late-adulthood, are characterized by physical and cognitive decline. Alterations in functional connectivity, measured via functional magnetic resonance imaging (fMRI), have been observed in suicidal, Parkinson's, Huntington's, and Alzheimer's disease populations. The review aims to explore the reliability of functional connectivity as a biomarker of suicide risk in several neurodegenerative disease populations.

Methods: A literature search of PubMed and Science Direct was conducted on Covidence from January 2000 to October 2023 to investigate the reliability of functional connectivity metrics as biomarkers of suicide risk in people with neurodegenerative diseases. 2,626 articles were yielded, and a total of 68 articles met the inclusion criteria.

Results: A variety of network and regional functional connectivity abnormalities were found to be consistent across study populations. Common network-wide alterations include the default mode network (DMN) and salience mode network (SN), and regional alterations include the posterior cingulate cortex (PCC) and anterior cingulate cortex (ACC).

Discussion: There is a clear gap in the literature in investigating connectivity signatures in Huntington's and suicidal populations, yielding two and five articles, respectively. Common functional connectivity signature alterations were found in individuals with Parkinson's and Alzheimer's disease. A lack of uniformity across studies, such as a variation in the type of fMRI functional connectivity analyses, measurement of functional connectivity, and a priori regions of interest limited the degree of confidence in the conclusions made from this review.

Conclusion: A literature review utilizing four search strategies was conducted to attempt to discover commonalities between the functional connectivity signatures associated with Alzheimer's disease, Parkinson's disease, Huntington's disease, and suicide risk. Despite discovering common signatures across some study populations, future research is needed to define a clear functional connectivity profile for DMN and SN alterations due to suicidality, independent of normal disease progression, in individuals with a neurodegenerative disease.

Keywords: functional connectivity; suicide risk; neurodegenerative disease; fMRI

Introduction

The increasing prevalence of neurodegenerative diseases is a growing concern, with approximately 50 million Americans affected, causing a significant burden to individuals, their families, and society [1]. Neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease, and Huntington's disease, are characterized by a progressive loss of neurons, resulting in a wide range of symptoms. Alzheimer's disease is a grey matter disease primarily affecting older adults and is the most prevalent form of dementia (93.58 cases per 100,00 people) [3, 102]. The disease is characterized by symptoms such as progressive memory deficits, myoclonic movements, psychotic episodes, and disruptive behaviors such as aggression [3]. These symptoms result from the accumulation of amyloid plaques and neurofibrillary tangles [3]. Parkinson's disease is the second most common neurodegenerative disease, with a prevalence of 13.43 cases per 100,000 people, which mainly affects older adults. The disease is characterized by symptoms such as bradykinesia, limb tremors, dystonia, and cognitive decline [2, 101]. The symptoms of Parkinson's disease result from the continuous formation of Lewy bodies beginning in areas such as the medulla oblongata and the olfactory bulb, eventually leading to widespread neurodegeneration [2]. Huntington's disease is a genetic neurodegenerative disease that results from an abnormal CAG repeat (36 or more) on chromosome

4p16.3 in the HTT gene [4]. It is characterized by symptoms such as chorea, dystonia, weight loss, and dementia [4]. The prevalence of the disease is 0.48 cases per 100,000 people and has a mean age of symptom onset of 30-50 years old [4, 100]. In Alzheimer's disease, Parkinson's disease, and Huntington's disease, aside from localized brain changes within the sites of neuronal loss, these diseases also impact connectivity patterns among remote brain regions [5].

Another worrisome societal concern is the increasing rates of suicide and suicidal ideation and behaviors [6]. The identification of biomarkers for suicide risk is a chief concern, leading to research isolating brain imaging signatures of suicidal ideation and behaviors [7, 8]. Neurodegenerative diseases are highly comorbid with psychiatric symptoms, including suicidal behaviors. An estimated 59% of adults with a neurodegenerative disease report serious depressive symptoms [9, 10]. 10% of people with Parkinson's disease and 21% of individuals with Huntington's disease report suicidal ideation. Suicide risk is also reported in Alzheimer's disease, especially in the early stages of the illness [11].

One potential biomarker for brain-based diseases, such as neurodegenerative and psychiatric diseases, is changes in functional connectivity among brain regions. Functional connectivity is defined as the strength of a connection between two distinct brain regions over a period of time while either at rest or during specific mental states. Functional magnetic resonance imaging (fMRI) measures the functional connectivity of distinct brain regions through the analysis of blood-oxygenation-level-dependent (BOLD) signals [12]. Specific groups of brain areas which demonstrate a consistent pattern of co-activation are called networks, and this analysis can be useful in predicting symptom onset within people with neurodegenerative diseases [12]. Furthermore, resting-state fMRI data is particularly useful in representing certain populations that may struggle in completing a task-based fMRI, and can provide insight into the spontaneous alterations in neural networks, resulting in a natural progression of neurodegeneration [40]. Certain disease states may implicate activity in these networks, which can be detected using fMRI. The benefit of fMRI analysis is the ability to distinguish two types of alterations: within or between networks. Within network functional connectivity alterations are classified as a region or network that can have functional connectivity alterations within the bounds of the area. Between network functional connectivity changes are known as functional connectivity alterations within several regions/networks that have a known influence on the other.

One example of a brain region that has shown abnormal activity in both neurodegenerative diseases and suicidality is the default mode network. The default mode network (DMN) is comprised of several brain regions and can be split into the anterior and posterior DMN (aDMN, pDMN) [16]. The aDMN consists of the medial prefrontal cortex (mPFC), dorsal medial prefrontal cortex (dmPFC), the anterior and posterior cingulate cortex (ACC, PCC), the anterior temporal lobe, the inferior frontal gyrus, and the lateral parietal cortex [16]. The pDMN consists of the PCC, precuneus, posterior inferior parietal lobule, hippocampus, and temporal lobe [16]. In depressed individuals, hyperconnectivity alterations within the DMN may present symptoms such as an increase in depressive ruminations, and hypoconnectivity may be characterized by symptoms such as an inability to engage in goal-directed behaviors [98, 99]. These differences in functional connectivity alterations within one network and between several networks is what can produce alterations in additional regional and network-wide functional connectivity patterns, which can be observed in fMRI data in various populations.

Despite the increased risk of suicidality in people with neurodegenerative diseases, there is still a lack of literature exploring alterations in functional connectivity as a predictor of suicide risk in people with neurodegenerative diseases. This research gap may result in treatment protocols that fail to encompass all needs of these populations such as primarily focusing on controlling symptoms related to cognitive or physical decline while neglecting mental health or psychiatric concerns. The present narrative review will explore the reliability of functional connectivity alterations as a biomarker of suicide risk in neurodegenerative disease populations. Specifically, we will focus on Alzheimer's disease, Parkinson's disease, and Huntington's disease, and review established functional connectivity signatures in these populations. We then review evidence of functional connectivity signatures in people with suicidal ideation or documented attempts of suicide. The results of this review indicate that the default mode network is altered in neurodegenerative populations, and more research is required to refine the current understanding of the development of suicidal behaviors/ideation in Alzheimer's, Parkinson's, and Huntington's disease.

Methods

A comprehensive literature search was conducted in PubMed and Science Direct databases from January 2000 to October 2023. The search was restricted to the English language and open access articles. A literature review with two main search strategies was conducted, one focusing on the functional connectivity patterns related to suicide risk, and the other on functional connectivity patterns related to neurodegenerative disease. The following neurodegenerative diseases were considered in this review: Alzheimer's disease, Parkinson's disease, and Huntington's disease. We included observational studies, both longitudinal and cross-sectional, and excluded any type of clinical/intervention trial and review, including meta-analyses and literature/scoping reviews.

Search Strategies – Functional Connectivity and Suicide Risk

The following search terms were applied for functional connectivity and suicide risk in PubMed and Science Direct: suicide risk OR suicide OR suicidality OR suicide risk OR suicidal behavior AND functional connectivity OR brain connectivity OR resting state OR fMRI OR functional magnetic resonance imaging. The search terms varied slightly for Science Direct but did not exclude any potentially relevant studies. Covidence was then used to screen for relevance based on title and abstract of the articles.

Search Strategies – Functional Connectivity and Neurodegenerative Disease Development

The following search terms were applied for functional connectivity and neurodegenerative disease in PubMed: functional connectivity OR brain connectivity OR resting state OR fMRI OR functional magnetic resonance imaging AND [insert disease name]'s disease OR [insert disease name]'s. The search terms varied slightly for Science Direct but did not exclude any potentially relevant studies. Similarly, Covidence was used to screen for relevance based on title and abstract of the articles.

Selection Criteria

The following inclusion criteria was used in the screening process: (1) studies must specifically include suicidality, both ongoing and in remission; (2) participants in the studies must be 18 years or older; (3) participants included in neurodegenerative disease studies must have a confirmed diagnosis of Alzheimer's, Parkinson's, or Huntington's disease; (4) functional connectivity must be measured via resting-state fMRI. Exclusion criteria included: (1) articles that were not in English; (2) articles that used non-human samples/participants (both cadaver and animal); (3) studies that included only participants that were relatives of people with Alzheimer's, Parkinson's, or Huntington's disease or were simply genetic carriers of any of the diseases.

Results

Our search yielded 2,626 articles. After a single-reviewer abstract screening, 130 studies were deemed relevant for full-text review, and 62 articles were eventually excluded. The results of the literature review are compiled in PRISMA flowchart in Figure 1. A total of 68 articles are included in the present review (Figure 2).

A summary of the study characteristics, including participant demographic information (e.g., age, sex, disease duration/years until onset) and main results of the fMRI functional connectivity analyses are presented in Supplementary Table 1 (see appendix).

Three articles that were included in the present review did not reveal a significant difference in functional connectivity between healthy controls and study populations. The remainder of the included studies found some degree of abnormal functional connectivity in study groups. Functional connectivity alterations are defined as an increase or a reduction of neuronal communication in dispersed neural networks or between specific regions of interest relative to a comparison group, such as healthy controls or participants with a less severe disease manifestation. A variety of experimental methods are reported across studies. Namely, studies differ in terms of the type of fMRI functional connectivity analysis used, such as regional homogeneity (ReHo), independent component analysis, and amplitude of low-frequency fluctuation (ALFF), the measurement of functional connectivity (e.g., dynamic or static functional connectivity) and the regions of interest under investigation.

Functional connectivity can be measured statically or dynamically. Static functional connectivity is the single measurement of connectivity across the entirety of the analysis, whereas dynamic functional connectivity considers changes in functional connectivity over time during the duration of the imaging [13]. Only seven articles measured dynamic functional connectivity within their study populations, six of which were investigating changes in people with Parkinson's disease, the other analyzing functional connectivity changes in individuals with Alzheimer's disease. The manner of interpreting the results varies based on the functional connectivity measurement. For example, in a study conducted by Schumacher et al., dynamic functional connectivity was assessed to identify how much time each participant spends in a specific brain state, which is associated with the functional connectivity status of a certain network(s) [58]. Cha and colleagues measured static functional connectivity, and the results consist of alterations in functional connectivity over a brief period [47]. These variations in functional connectivity measurements may challenge the ability to generate a conclusion about the overall connectivity patterns within study populations.

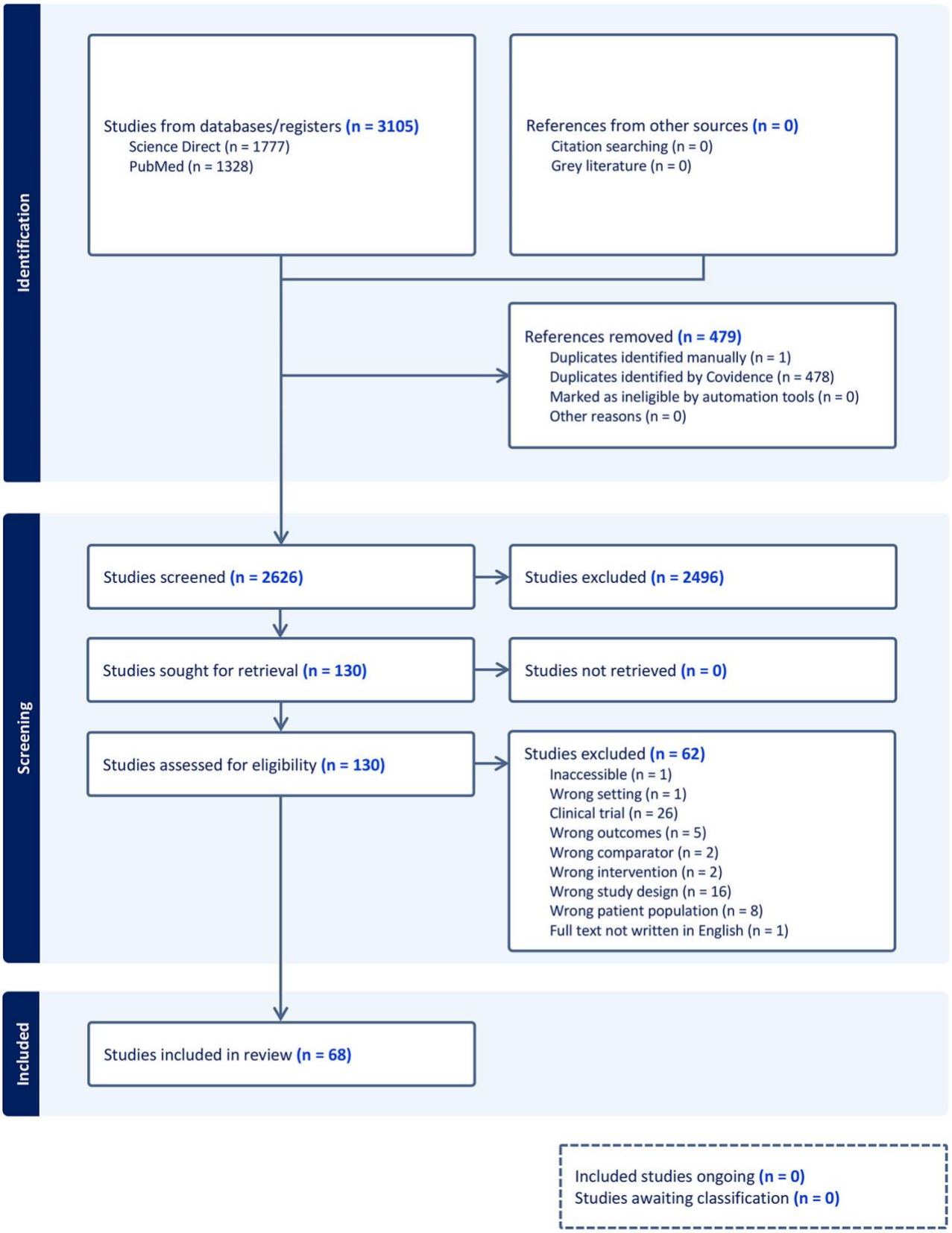

Figure 1. A PRISMA flow diagram of the present narrative review. Figure created with Covidence.

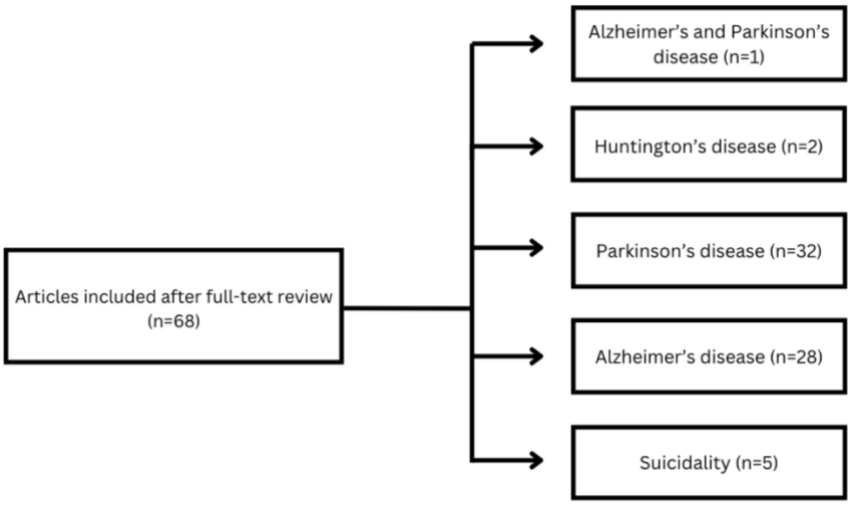

Figure 2. A flow diagram of the article grouping by study population. Created by the author using Canva.

Alzheimer's Disease

Previous studies consistently report reductions in functional connectivity within the default mode network (DMN) in adults with Alzheimer's disease relative to patterns expected in the general population [14, 15]. 17 studies report alterations in the DMN [41, 42, 44, 45, 47, 49, 50, 55, 57, 58, 60, 61, 63, 64, 65, 66, 67]. While there is ample evidence implicating functional connectivity changes in the DMN in Alzheimer's disease, there is inconsistent findings regarding the exact nature of these changes. For example, some studies report reduced within network-level DMN activation in people with Alzheimer's compared to controls [44, 45, 49]. However, one study reported enhanced DMN activation in people with Alzheimer's when compared healthy controls and patients with mild cognitive impairment (MCI) [50]. This study also observed an increase in activation specifically within bilateral medial prefrontal cortex and precuneus in individuals with Alzheimer's compared to controls and the MCI group, and a relative reduction in activity in the precuneus and dorsal anterior cingulate cortex in people with Alzheimer's compared to controls [50]. More research is required to refine our current understanding of the specific ways in which Alzheimer's disease influences DMN functional connectivity. Other common networks that demonstrated reduced functional connectivity in the Alzheimer's disease populations include the somatosensory (SMN), auditory (AUD), visual (VIS), and salience (SN) networks. Many of the reviewed studies reported reductions in connectivity in the VIS [41, 42, 55, 57, 58, 63, 67], followed by reductions in the SMN [42, 57, 63, 67] and the AUD [41, 55, 67]. At the level of individual brain regions, six studies specifically reported a reduction of functional connectivity within either the anterior cingulate cortex (ACC) [50, 51, 53] or the posterior cingulate cortex (PCC) [47, 49, 54]. Two studies reported reductions in both the ACC and PCC [43, 52]. Other studies observed reduced connectivity within the superior frontal gyrus (SFG) [36, 46, 48, 51, 52] and within the hippocampus [54, 56, 59]. These areas are responsible for cognitive processing and memory formation/retention. Reduced connectivity within these regions may be attributed to neuronal degeneration that is consistent with normal disease progression, but it could also be attributed to suicidality. Ultimately, it is evident that more research is required to refine our current understanding of DMN and other network/regional functional connectivity alterations, and how it may vary by population.

Parkinson's Disease

Many of the reviewed studies report reduced functional connectivity in the DMN in individuals with Parkinson's disease. An additional network of interest is the SN. The SN consists of the anterior insula, anterior cingulate cortex (ACC), and ventral striatum [17]. This network functions as a bridge between the DMN and the frontoparietal network and contributes toward executive control. The SN is activated during the processing of competing reward and pain stimuli, thereby influencing motivation, emotional processing, and response selection [18]. Another network that is implicated in Parkinson's disease is the frontoparietal network (FPN). The FPN is responsible for organizing behavior to formulate and carry out goals. Functional connectivity abnormalities in the SN and DMN was found in articles on Parkinson's disease regardless of the type of region of interest for the fMRI scan. Studies that conducted whole-brain fMRI scans with no intentional preliminary region of interest and studies that conducted specific functional connectivity fMRI analyses on the SN and DMN both found conflicting results. Five studies found decreased connectivity within DMN [72, 75, 92, 93, 96], and two found decreased connectivity between the DMN

and other networks [78, 79]. Two studies reported increases in connectivity within the DMN [38, 81], and four found increases between the DMN and other networks [37, 77, 90, 95]. In the SN, one study found a rise in activity within the network [81], and other reported a decrease in connectivity within the SN [75]. Two additional studies described a decrease in functional connectivity between the SN and other networks [79, 90].

Studies also observed reductions in functional connectivity within other networks including the SMN and VIS, which was also observed in studies on Alzheimer's disease. These reductions in functional connectivity may be due to normal disease progression in Parkinson's disease.

At the regional level, similar to the findings of the Alzheimer's disease articles, the ACC and PCC demonstrated significantly different connectivity profiles compared to healthy controls. Altered activity in the ACC and PCC was observed in studies examining entire networks (e.g., DMN and SN) [37, 38, 72, 75, 78, 81, 90, 92, 93, 95, 96] or in a priori analyses of specific brain regions [37, 68, 72, 75, 77, 78, 79]. A notable four articles noted hypoconnectivity between the anterior cingulate cortex with other regions such as dorsal anterior insula, left lateral parietal cortex, and the left middle frontal gyrus [77, 78, 79]. The putamen also demonstrated functional connectivity differences relative to healthy controls. In several of the reviewed studies, the putamen demonstrated a reduction in within-region connectivity [69, 83, 84, 88] and reduced connectivity between other regions, such as the cerebellum [73], hippocampus [73], and anterior prefrontal regions [86]. In other reviewed studies, the putamen demonstrates hyperconnectivity with parafascicular nucleus [39], medial parietal cortex [86], and right rolandic operculum [73]. These alterations in the connectivity within the putamen in the reviewed studies support the accepted relationship between putamen functional connectivity alterations and Parkinson's disease [19]. This means that the connectivity between a certain region and the putamen could be hyperactivated and the connectivity between the putamen and another region could be hypoactivated, and both types of connectivity alterations could support the development of motor symptoms associated with Parkinson's disease.

Due to Parkinson's disease being classified as a multi-system neurodegenerative disease, we expected various brain networks to exhibit faulty functional connectivity [2]. Several studies supported this expectation, including a study completed by Díez-Cirarda and colleagues (2017), where they compared people with Parkinson's disease and controls, and found reductions in network-level between connectivity in the SMN and cognitive control network (CCN), between the SMN and VIS, between the SMN and AUD, between the CCN and VIS, and between the subcortical network and DMN. Ultimately, additional research is needed to clarify how we can generalize these results to inform our understanding of disease progression.

Huntington's Disease

The results of the two studies on Huntington's disease do not indicate a clear trend in connectivity profiles associated with the illness. One article reported significant reductions in the DMN [20] and the other did not [21]. However, both studies did report reductions in ACC functional connectivity. One reported ACC functional connectivity reductions within the DMN [20], and the other reported reduction in the ACC within the dorsal attention network (DAN) [21]. The DAN is comprised of the intraparietal sulcus and frontal eye fields of both hemispheres [22].The DAN regulates signals from top-down sensory regions, including visual, auditory, olfactory, and somatosensory association cortices, to mediate attention towards relevant stimuli [22, 23].

Additional notable results from Dumas and colleagues (2013) include reduced functional connectivity between the medial visual network in the left frontal lobe and the right parietal lobe in participants who have early stages of Huntington's and in people who have pre-symptomatic Huntington's versus controls. They also observed reduced functional connectivity between the medial visual network and the cingulate gyrus within the DMN in individuals who have pre-symptomatic Huntington's versus controls. When comparing people who have early stages of Huntington's to individuals with pre-symptomatic Huntington's, there was a decrease in functional connectivity between the medial visual network and the superior occipital lobe, the putamen, the globus pallidus, the thalamus, and bi-lateral orbital frontal cortex. Finally, when comparing adults with early stages of Huntington's and controls, there was reduced functional connectivity within the left parietal lobe, between the pre-frontal cortex and the DMN, and between the central executive network and thalamus and left supramarginal gyrus.

Suicidality

Five articles reported on functional connectivity signatures of suicidality as measured by resting-state fMRI. Four articles described alterations in functional connectivity in a priori regions of interest [24, 25, 26, 27]. One article described network-level increased functional connectivity patterns and observed alterations within the ACC as a component within the frontal-limbic network [28]. One article observed reductions in functional connectivity between the habenula and DMN [27]. The habenula, located within the epithalamus, is related to emotional, motivational, and reward processes; and its dysfunction is associated with other mood disorders, such as depression and schizophrenia [34]. Other regions of interest that demonstrated significantly reduced functional connectivity in suicidal populations include the somatosensory-motor cortex [24], ventrolateral prefrontal cortex and orbitofrontal cortex [25], and inferior frontal gyrus [24, 26]. There was a similar decrease in functional connectivity in the orbitofrontal cortex in people with Huntington's disease [20]. The somatosensory cortex is

responsible for processing somatosensory input and coupling sensory and motor signals to generate subsequent movements [29]. The ventrolateral prefrontal cortex is associated with executive functions, such as maintaining attention [30]. The orbitofrontal cortex controls stimulus-reinforcement association learning, and the inferior frontal gyrus is associated with language processing and production but has also been implicated in reductions in impulse control and a lack of risk aversion [31, 32, 33].

Additional results found by Wagner et al., (2019) include heightened functional connectivity between the left habenula and the left precuneus cortex and the right precentral gyrus (patients with treatment-resistant depression (TRD) versus treatment-sensitive depression (TSD)). They also found increased connectivity between the left habenula and right precuneus cortex (TRD populations versus TSD individuals and controls), and decreased connectivity in people with TSD versus controls, but it increases with higher levels of suicidal ideation.

It is worth noting that one article concludes that there was a reduction in the hippocampus [26] functional connectivity in suicidal populations, which was also seen in Parkinson's disease populations [73]. This pattern of functional connectivity may be a future avenue of research in determining the shared contributors of increased and debilitating psychiatric symptoms.

Discussion

According to the findings of this review, altered functional connectivity in the DMN, followed by the SN, VIS, and SMN, is the most common finding across the four populations of interest. The DMN, which is activated during future-oriented thought processes, self-referential processing, and autobiographical memory retrieval, has been linked to suicide [16]. Suicidality is associated with anxiety and persistent negative thoughts about oneself and future [16]. Therefore, alterations within this networks are consistent with the symptoms of suicidality. However, alterations in DMN activity can also represent the impact of neurodegeneration, which eventually results in the onset of various motor and cognitive symptoms. The SN is linked to emotional responses to stimuli and subsequent behavior. This network may also be linked to suicidality due to its between-network connectivity to the DMN [18]. Studies also observe decreases of functional connectivity in the ACC and PCC, which is consistent with the finding of alterations in both DMN and SN across disorders, as the ACC and PCC are represented in both neural networks. In addition to being linked to suicidal ideation and behaviors in the reviewed studies, alterations in both neural networks have been mainly reported in people with Alzheimer's and Parkinson's disease.

The findings of disrupted functional connectivity in the DMN and SN, via the ACC and PCC, in several neurodegenerative disease and suicidal populations provides insight into how the development of psychiatric symptoms might result from degeneration in these networks [35]. Huntington's disease might be associated with the same functional connectivity alterations in DMN and SN as is observed in Alzheimer's and Parkinson's disease progression, but more research is required to confirm this.

Several limitations exist within the literature which challenge the ability to make conclusions about the relationship between functional connectivity, neurodegenerative disease, and suicidality. Firstly, studies in neurodegenerative populations do not always control for the presence or degree of depressive symptoms in their analyses despite known comorbidity. This may result in the misinterpretation of the true extent of dysfunctional connectivity. It is worth mentioning that only some Alzheimer's and Parkinson's disease articles explicitly included individuals with depression [36, 37, 38, 39]. Additionally, studies differed in terms of their experimental designs and hypotheses. Some studies investigated regional brain functional connectivity differences, while others were network-wide (e.g., hypoactivity between the bilateral inferior parietal lobe and superior parietal lobe vs. hyperactivity in the DMN). Since there is some overlap of brain regions between different networks, meaning certain regions are implicated in the connectivity in multiple networks, this disconnect between articles proved to be a challenge when assessing common trends across the literature.

There are also methodological limitations with this review, including the review's focus on resting-state fMRI to quantify functional connectivity, and many excluded studies utilized other measurements of functional connectivity, including magnetoencephalography (MEG) and electroencephalography (EEG). Therefore, some relevant findings may be missing from this analysis due to this exclusionary reason. Additionally, the exclusion of task-based fMRI may have also limited the scope of the conclusions that were made. Resting-state fMRIs do not provide a complete understanding of which brain regions are experiencing functional connectivity disturbances in the study populations, as some alterations may only manifest when performing clinically relevant cognitive or affective processes. Furthermore, a single reviewer conducted the abstract and full-text reviews to determine eligibility of the included articles, thereby increasing the risk of potential bias or inaccuracy during reviewing.

The type of fMRI functional connectivity analyses used also differed across studies. While all articles used voxel-based variables derived from BOLD fMRI signals, specific variations in analyses are listed in Table 1. These differences in the type of fMRI functional connectivity analyses may contribute to more difficulty in establishing a common trend between articles. Each type of analysis contains its own set of advantages and limitations. ALFF and fractional amplitude of low-frequency fluctuation (fALFF) measure regional brain activity, with ALFF measuring the absolute density of brain activity, whereas

fALFF measures the density of brain activity in proportion to the region [40]. Both measures do not measure functional connectivity between various brain regions, which is a crucial limitation when trying to make conclusions about network-based alterations [40]. ReHo measures the degree of time-series similarities between voxels and a primary limitation is restriction of regional measures, rather than examining network-based or whole-brain functional connectivity measurements [40]. Individual component analysis (ICA), which is a common functional connectivity measurement, utilizes multivariate decomposition to isolate the BOLD signals into various functional networks and forms spatial maps of the networks [40]. A limitation of ICA is the inability to consistently distinguish the boundaries of certain networks, with one network potentially being broken down into several unnecessary networks [40].

Ultimately, the associations found of network-scale functional connectivity alterations in suicidal and neurodegenerative disease populations suggest that functional connectivity analyses should be considered when attempting to determine the best course of neurodegenerative disase treatment. The observation of functional connectivity alterations will serve future clinicians in determining the best methods of palliative and curative care. No known cure exists for Alzheimer's, Parkinson's, or Huntington's disease, and most ongoing research is dedicated to monitoring the symptoms associated with physical and cognitive decline. Addressing the debilitating psychiatric symptoms of this underserved research population is a growing need. As discussed previously, the DMN is altered in neurodegenerative populations and in some suicidal populations. More research is required to develop a robust understanding of what extent the DMN alterations are due to normal disease progression, rather than suicidality. Extensive caution needs to be taken during future research to determine what is the functional connectivity signature of developing suicidality symptoms and how it can be isolated from alterations due to cognitive impairment and normal disease progression. Due to the apparent overlap in functional connectivity alterations throughout the study populations, more work needs to be done to specifically isolate suicide risk in people with neurodegenerative diseases. Future research of this topic will hopefully yield more information as to if there are specific or unique functional connectivity signatures of suicidality in neurodegenerative populations. Through the continuous push to investigate the role of DMN and SN, including the PCC and ACC, functional alterations in neurodegenerative disease populations, any future work may inform future care by physicians and mental health professionals. This future care can include personalizing medicine and developing a better understanding of the risks these populations face, thereby reducing suicide rates in these populations.

Conclusions

A total of four search strategies were used to conduct a literature review to describe the functional connectivity signatures associated with Alzheimer's disease, Parkinson's disease, Huntington's disease, and suicide risk. The aim of this review was to determine the reliability of utilizing functional connectivity as a reliable biomarker of suicide risk in these neurodegenerative diseases. The default mode network (DMN), followed by the salience network (SN), was found to have significant alterations in functional connectivity in most study populations. Therefore, alterations in functional connectivity may stand to be a viable measure of suicide risk in Alzheimer's and Parkinson's populations. Future research should be geared toward expanding upon the role of DMN and SN in neurodegenerative disease progression. While significant resources are poured into investigating the progression of motor and cognitive symptom of Parkinson's, Huntington's and Alzheimer's disease, more emphasis needs to be made on psychiatric symptoms, including suicide risk, to accurately care for people diagnosed with these neurodegenerative diseases.

List of Abbreviations

MEG: magnetoencephalography
EEG: electroencephalography
ReHo: Regional homogeneity
ICA: independent component analysis
DMN: default mode network
SN: salience network
BOLD: blood-oxygenation-level-dependent
aDMN: anterior DMN
pDMN: posterior DMN
mPFC: medial prefrontal cortex
dmPFC: dorsal medial prefrontal cortex
ACC: anterior cingulate cortex
PCC: posterior cingulate cortex
DAN: dorsal attention network
FPN: frontoparietal network
SMN: somatosensory network
CCN: cognitive control network
AUD: auditory network
VIS: visual network
SFG: superior frontal gyrus
fMRI: functional magnetic resonance imaging
ALFF: amplitude of low-frequency fluctuation
fALFF: fractional amplitude of low-frequency fluctuation

Conflicts of Interest

The author(s) declare that they have no conflict of interests.

Authors' Contributions

NAB: made substantial contributions to the design of the study, the collection of data as well as interpretation and analysis of the data, drafted the manuscript, and gave final approval of the version to be published.

Acknowledgements
I am sincerely thankful for the invaluable advice that my mentor, Micaela Wiseman, gave to me during the process of devising and writing this literature review. Her contributions to the study design and manuscript revision were critical to the successful completion of this review.

Funding
This study was not funded.

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Article Information
Managing Editor: Jeremy Y. Ng
Peer Reviewers: Micaela Wiseman Ricky Chow
Article Dates: Received Dec 16 23; Accepted Mar 26 24; Published May 07 24

Citation
Please cite this article as follows:
Bovin NA. The reliability of functional brain connectivity as a biomarker in the prediction of suicide risk in neurodegenerative disease populations: A literature review. URNCST Journal. 2024 May 07: 8(4).
https://urncst.com/index.php/urncst/article/view/572
DOI Link: https://doi.org/10.26685/urncst.572